providing an apparatus for intracardiac drug administration comprising a catheter, said catheter having at least one position sensor which generates signals responsive to an applied field for determining the position and orientation of said catheter, said signals being used to generate position and orientation coordinates, and a drug delivery device for delivering said cell;

inserting said catheter into a chamber of said heart at a site;

delivering said cell to said site with said drug delivery device based on position and orientation coordinates in response to said signals from said position sensor.

REMARKS

Claims 1-40 are in the case and presented for reconsideration. Claim 1 has been amended. The support for the amendment can be found in the Applicant's Specification, for example, page 26, line 4-8. No new matter has been added.

Claims 1, 2, 12-15 have been rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 6,283,951 (Flaherty et al.). With respect to this rejection, the Examiner has stated:

> Flaherty discloses systems and methods that use the cardiovascular system as a conduit to deliver drugs, such as therapeutic drugs, genes, growth factors and the like, directly to selected tissue regions within the body. (Col. 1, line 10-15) "Drug" as defined herein includes any therapeutic drugs, genetic materials, growth factors, cells, e.g. myocites, vectors carrying growth factors, and similar therapeutic agents or substances that may be delivered within a patient's body for any therapeutic, diagnostic or other procedure. In one aspect of the present invention, a transvascular catheter system is provided that generally includes a catheter, a drug delivery element, an orientation element, and possibly a puncturing element and/or an imaging element. (Col. 3 line 54-62)
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> When the puncturing element is being oriented, the orientation element is imaged. The imaging element is preferably operated to obtain an image of the orientation element in relation to the surrounding tissue, thereby identifying the ordination of the puncturing element because of the predetermined relationship between the orientation element and the puncturing element. (Col.5, lines 18-25) This imaging may be considered a sensor; it is a well-known fact that the optical system in the human body is referred to as one of the sensors in the body because it is capable of generating "position and orientation coordinates". The imaging element of this apparatus is also capable to providing position and orientation coordinates information, therefore it could be considered a sensor.

Accordingly, the Applicant would like to take this opportunity to outline the particular teaching of Flaherty et al. Flaherty et al. describes systems and methods for delivering drugs to selected locations within the body. The term "drug" is described to include cells, such as myocites. Col. 3, lines 53-56. The "orientation element" described in Flaherty et al. is not a position sensor capable of generating signals responsive to an applied field for determining the position and orientation of the catheter. But rather, the "orientation element" is either a "cage structure that includes a plurality of struts extending axially along the distal portion" of the catheter (in one embodiment), or "a marker that may be imaged using an external imaging system, and preferably a pair of markers disposed opposite one another on the periphery, either instead of or preferably in addition to the cage structure." Col. 4, lines 50-64. Thus, the "orientation element" of Flaherty et al. is entirely incapable of being used as a position sensor

which generates signals responsive to applied field for determining the position and orientation of the catheter. Moreover, Flaherty et al. clearly does not describe, suggest or infer utilizing a position sensor which generates signals responsive to an applied field to generate position and orientation coordinates such as found in the Applicant's claimed invention (as amended).

Accordingly, the cage or visible marker of the Flaherty et al. device can only be used to determine the orientation of the puncturing element, i.e. orientation in relation to the surrounding tissue. Col. 5, lines 13-23. Additionally, the Flaherty et al. device must utilize an imaging device, i.e. an ultrasound transducer, which takes images, "preferably including the orientation element, the selected tissue region, and/or other landmarks within the vessel or the surrounding tissue." Col. 5, lines 18-23. Thus, based on this imaging technique, only the orientation of the puncturing element can be determined which is due to the imaging of the surrounding anatomical landmarks. Clearly, the orientation element and imaging element combination of Flaherty et al. simply does not address or suggest generating signals responsive to an applied field for determining the position and orientation of the catheter wherein the signals are used to generate position and orientation coordinates and wherein the cell is delivered to a site within the heart (with the drug delivery device) based on the position and orientation coordinates.

Moreover, the Applicant respectfully disagrees with the Examiner's statement that the imaging taught by Flaherty et al. "may be considered a sensor" and that "it is a well-known fact that the optical system in the human body is referred to as one of the sensors in the body because it is capable of generating 'position and orientation coordinates'." The Applicant notes that no specific data nor support as well as nothing in the record has been shown in order to substantiate this alleged "well-known fact". Accordingly, the Applicant respectfully requests that the Examiner provide an affidavit in accordance with 37 C.F.R. § 1.104 (d) (2) and MPEP § 2144.03 in order to substantiate. Accordingly, for the reasons outlined above, Claim 1 (Amended) is not anticipated by Flaherty et al., nor is it rendered obvious by this reference.

Claims 3-11 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Flaherty in view of U.S. Patent 5,865,738 (Morocos et al.). With respect to this rejection, the Examiner has stated:

> As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Flaherty, however does not teach a method of

> assessing the viability of the heart. Morocos discloses a method and apparatus for evaluating the viability of a tissue of interest, particularly that presents as dead but may be merely stunned or hibernating with reduced or no obvious activity, such as contractility (abstract).
>
> This apparatus is carried at the tip of a catheter, which can be guided inside the heart during cardiac catheterization. The new probe allows the physician to: 1) position the probe at a tissue of interest, 2) evaluate the initial state of the tissue, 3) diffuse into the tissue basic ingredients needed for cellular respiration and resulting energy production (oxygen, oxygen-releasing substrates, glucose, low energy phosphates); 4) detect the result of this process by measuring substance uptake, oxygen utilization and/or oxidation reduction (redox) stores of the respiratory enzymes; and 4) optionally detect consequent mechanical activity by ultrasound backscatter technique (in conjunction with a second catheter). (col.9, line 31) This apparatus allows a one to plan in detail (definition of mapping as found in dictionary was plan in detail) where the damaged tissue was located, and when a myocite or a myoblast should be delivered. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combine the two teaching, since according to Morocos cardiologists and cardiac surgeons would both benefit from a procedure which would identify cardiac tissue which has a good probability of returning to normal function. (Col.5, line 60) Faced with the recognition of widened variety of ischemic clinical pictures with variable degree of retained viability, and armed with the knowledge that several conditions previously considered hopeless can now be salvaged if appropriately recognized as viable, cardiologists and cardiac surgeons are increasingly aware of the need to optimize selection form their ever-widening choice of techniques in a way that matches the particular clinical situation. (Col.2 line 10-20)

As outlined by the Examiner, Morocos teaches a very specific and complex method and apparatus for evaluating the viability of a tissue of interest. This includes "1) position the probe at a tissue of interest, 2) evaluate the initial state of the tissue, 3) diffuse into the tissue basic ingredients needed for cellular respiration and resulting energy production (oxygen, oxygen-releasing substrates, glucose, low energy phosphates); 4) detect the result of this process by measuring substance uptake, oxygen utilization and/or oxidation reduction (redox) stores of the respiratory enzymes; and 4) optionally detect consequent mechanical activity by ultrasound backscatter technique (in conjunction with a second catheter)."

It is important to note that the Morocos et al. tissue viability apparatus and method for assessing viability of tissue is not at all compatible with the method of the Applicant's claimed present invention (a combination of Claims 1, 2 and 3). As described in detail in the Applicant's Specification, viability is identified through a viability map in accordance with the Applicant's

not claimed.

teaching on Page 9, line 9 – Page 10, line 10. This also includes generating a geometrical map of the heart indicating local viability levels wherein ischemic areas to be treated are marked on the map with a grid of points and wherein the map and grid are determined based on physiological activity of the heart indicative of local tissue viability gathered in conjunction with location coordinates. It is important to note that the tissue viability apparatus and method described in Morocos et al., even in combination with the system taught by Flaherty et al. is entirely incapable of achieving the Applicant's claimed invention of Claims 3-11.

Thus, there is absolutely no physical compatibility that can be found that would lead one of ordinary skill to combine Flaherty et al. and Morocos et al. in the manner suggested that could ever arrive at the Applicant's claimed invention of Claims 3-11. Additionally, based on the very complex procedure for evaluating viability of tissue as taught by Morocos et al., this references actually teaches away from the Applicant's claimed invention of Claims 3-11 since they are entirely distinct and unrelated.

Moreover, the Examiner's use of a dictionary definition of the word "mapping" is clearly an improper use of extrinsic evidence outside of the four corners of the Applicant's Specification and in conflict with established practices set forth in MPEP § 608.01 (o) as well as established legal precedent. It is important to note that Applicant has more than adequately defined "mapping" in accordance with the present invention as detailed in the Applicant's Specification, for example, page 9, line 9-page 10, line 7; page 26, line 17-page 27, line 2 and page 41, line 12-page 42, line 42.

Claims 16-17, 25-31 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Flaherty et al. as applied to Claim 1, and further in view of U.S. Patent 6,277,082 (Gambale et al.). With respect to this rejection, the Examiner has stated:

> As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Flaherty, however, does not teach a catheter which utilizes a laser to create a channel at an oblique angel were the said cells would be delivered. Gambale discloses an invention provides devices and methods for detection of ischemic biological tissue by temporarily altering the temperature of the tissue. (Abstract) Gambale also discloses a detection of an ischemic area of tissue may be followed by a treatment, which may include the implantation of an angiogenic implant alone or in conjunction with a therapeutic agent, such as a growth factor to promote angiogenesis or a cell or gene therapy substance to initiate regeneration of the subject tissue. In such cases, the obturator is adapted to penetrate the tissue in order to facilitate the placement of

> the angiogenic implant into the tissue alternatively the treatment may comprise creation of channels in the ischemic region by mechanical or laser energy. (col.3, line 40-50) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention as made to have included the teaching of both Flaherty and Gambale, because according to Gambale if the tissue has remained viable despite the previous deprivation of blood, revascularization, or the restoration of blood flow, to dormant or hibernating tissue can restore the muscle's normal function. (Col.1, line 5-10) Injection of growth factor into myocardial tissue initiates angiogenesis at that site, which is exhibited by a new dense capillary network within the tissue accurate diagnosis and identification of ischemic areas is essential to proper treatment. (Col.2, Line 5-25)

As outlined above, it is the Applicant's position that Flaherty et al. neither describes or suggests a method for delivering a cell to the heart of a patient using a catheter having at least one position sensor which generates signals responsive to an applied field for determining the position and orientation of the catheter wherein the signals are used to generate position and orientation coordinates and the cell is delivered to a site of the heart based on the position and orientation coordinates in response to signals from the position sensor. Additionally, it is also important to note that Gambale is directed solely to an ischemia detection system and method wherein the temperature of a section of tissue is altered temporarily by either warming or making colder than normal and then recording and displaying the thermal profile over time for the tissue as it returns to its normal temperature. Col. 2, lines 61-65.

Additionally, Gambale does not address in any manner utilizing a method for delivering a cell (such as claimed in Amended Claim 1 and Claim 16) wherein the cell is capable of cell fusion with other cells; and wherein the cell fusion results in myogenesis (Claim 17). It is also important to note that Flaherty neither describes nor suggests creating a channel for delivering cells utilizing laser (as found with Claims 25, 26, 27, 28, 29 and 30) as well as delivering the cell at an oblique angle (Claim 31). This is clearly acknowledged by the Examiner where it is stated on page 5 of the present Office Action as follows: "Flaherty, however, does not teach a catheter which utilizes a laser to create a channel at an oblique angle where the cells would be delivered." Moreover, it is acknowledged by the Examiner in the present Office Action on page 10, paragraph b. ii. where it is stated: "Gambale does not discuss the method of placing the cells into the ischemic detected tissue...." Accordingly, neither Flaherty nor Gambale, either alone or in combination with each other arrive at the Applicant's claimed invention as claimed in Claims 16-17 and Claims 25-31.

Claims 19-24 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Flaherty et al. in view of Gambale and further in view of U.S. Patent 6,258,789 (German et al.). With respect to this rejection, the Examiner has stated:

> As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Gambles discloses an ischemia detection system. However, neither Gambale nor Flaherty teaches the origin of the cell. German discloses cells of a mammalian subject, which are genetically altered to operatively incorporate a gene, which expresses a protein, which has a desired effect. (Abstract). One of the objects of German's method is to produce genetically transformed cells (genetically superior cell), which have incorporated in the their genome exogenous genetic material in the form of a fully functional gene which expresses biologically active and therapeutically useful protein that functions with in the cell. (col.3, line 34-39) any exposure of the DNA of the treated cell to the immune system can result in adverse reaction such as inflammatory reactions to the DNA administered. (Col.2 lines 53-60) Therefore, it would be beneficial to treat these cells with immunosuppressants prior to implantation.
>
> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention as made to have included the teaching of Gambale, Flaherty and German, because German simply expands on the origins of the cells in Flaherty and Gambale teachings. German is not specifically speaking of myocites, but nor are any of the claims 18-20.

The Applicant would like to point out that German et al. is directed solely to the delivery of gene products by intestinal cell expression wherein a formulation comprising nucleic acids (DNA, RNA, DNA-RNA Hybrids, oligonucleotides, and synthetic nucleic acids) are delivered into the gastrointestinal tract of a patient (*in vivo* gene therapy) in order to incorporate the nucleic acids into the epithelial cells of the intestine. Col. 3, lines 1-13; col. 9, lines 8-10. Additionally, German et al. describes delivery of the DNA via the mouth directly into the GI tract. Col. 9, lines 8-12. It is important to note that the unique *in vivo* gene therapy approach disclosed in German et al. is entirely distinct from the method steps of the claimed present invention (Claims 19-24). German et al. simply does not address, suggest or infer treating a cell prior to delivery (Claim 19 of the present invention); utilizing an immunosuppressant (Claim 20 of the present invention); harvesting the cell from the patient (Claim 21 of the present invention); treating the cell prior to delivery (Claim 22 of the present invention); utilizing a genetically superior cell (Claim 23 of the present invention) and utilizing a cell that is a

xenograft (Claim 24 of the present invention). Accordingly, neither Flaherty, Gambale nor German et al., either alone or in combination with each other describe, suggest or infer the Applicant's claimed invention of Claims 19-24. Accordingly, these claims are clearly not rendered obvious by these references.

Claims 33, 36 and 39 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Flaherty in view of Gambale, and further in view of U.S. Patent 5,960,796 (Kramer). With respect to this rejection, the Examiner has stated:

> As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Gambale discloses an ischemia detection system. However, neither Gambale nor Flaherty teaches a catheter with a device capable of providing a pressure burst. Kramer discloses a method of infusion of drug in to the bone marrow. It also teaches a monitoring over pressurization during high-pressure infusions or blocked fluid flow. These operations could be combined with a microprocessor-controlled system to automatically warn the operator of unsafe or otherwise unsatisfactory conditions. (Col.4, line 40) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention as made to have included the teaching of Gambale, Flaherty and Kramer, because according to Kremer this invention helps in monitoring over pressurization. Although Kramer's apparatus is for the use of the bone marrow but it is the concept behind a safety valve to monitor pressure that is relevant here. Kramer teaches why it would be important to utilize a pressure bust in any system not just in the bone marrow.

The Applicant would like to point out that Kramer is directed solely toward an implantable intraosseous device for rapid vascular access utlizing a needle assembly 12 and a pressure chamber 16 for rapidly accessing bone marrow (contained within bone) by directly puncturing the bone with the needle assembly 12. Col. 1, lines 22-25 and col. 6, lines 7-18. It is also important to note that Kramer is not only an intraosseous device entirely distinct from the device used with the Applicant's claimed invention, but also requires a substantial force in order to penetrate bone and access the bone marrow. This is addressed in Kramer where it states that the significant force is "any driving force sufficient to cause the needle assembly 12 to penetrate the surface of a bone..." Col. 6, lines 33-35. Thus, the pressure mechanism and driving forces provided thereby, as taught by Kramer et al., are completely different and unusable with the apparatus that is part of the Applicant's claimed method invention. Accordingly, the references cited above, even combined in a manner suggested, simply does not describe, suggest or infer the Applicant's claimed invention of Claims 33, 36 and 39.

Claims 34, 37 and 40 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Flaherty et al. in view of Gambale, and further in view of U.S. Patent 4,578,061 (Lemelson). With respect to this rejection, the Examiner has stated:

> As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Gambale discloses an ischemia detection system. However, neither Gambale nor Flaherty teaches teach a catheter with a retractable needle. Lemelson discloses a catheter with a retractable needle and method are provided for injecting a quantity of a liquid. (Abstract) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention as made to have included the teaching of Gambale, Flaherty and Lemelson, because according to Lemelson the needle need to be retractable so that it will not penetrate tissue as the device is worked through the body. (Col.1 line 40)

The Applicant does acknowledge that Lemelson discloses utilizing a needle that is retractable. However, since Flaherty et al., Gambale and Lemelson relate to unique inventions individually having no relation with each other and there is no specific teaching in any of these references that would lead one of ordinary skill to not only combine them, but also to combine them in a manner as suggested in an effort to arrive at the Applicant's claimed present invention, Claims 34, 37 and 40 of the Applicant's claimed present invention are not rendered obvious by these references.

Therefore, by this Amendment, and for the reasons outlined above, the claimed present invention is both patentably distinct and non-obvious over the cited prior art of record and favorable action is respectfully requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 1. (Twice Amended) A method for delivering a cell to a heart of a patient comprising the steps of:

providing an apparatus for intracardiac drug administration comprising a catheter, said catheter having at least one position sensor which generates signals responsive to an applied field for determining the position and orientation of said catheter, said signals being used to generate position and orientation coordinates, and a drug delivery device for delivering said cell;

inserting said catheter into a chamber of said heart at a site;

delivering said cell to said site with said drug delivery device based on position and orientation coordinates in response to said signals from said position sensor.